Cancer Mortality After Multiple Fluoroscopic Examinations of the Chest [1,2]

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ABSTRACT—Total cancer deaths were not increased among 2,074 women and 1,277 men who were fluoroscopically examined an average of 73 and 91 times, respectively, during lung-collapse therapy for tuberculosis (TB). Patients who did not receive this form of therapy (2,141 women and 1,418 men) and general population rates were used for comparison. All subjects were discharged alive from eight TB sanatoria in Massachusetts between 1930 and 1954; the average follow-up was 23 years. Deaths due to breast cancer were not increased among exposed females [standardized mortality ratio (SMR)=1.0, $n=24$], and SMRS greater than 2.1 could be excluded with 95% confidence. In contrast to other series, our inability to detect a breast cancer excess was likely due to lower breast doses (66 rad) and higher average ages at exposure (28 yr) and thus lower sensitivity. A deficit of lung cancer among exposed males and females was observed (SMR = 0.8)

TABLE 1.—*Gender and vital status as of January 1, 1981, as related to category of radiation exposure*

Status	Exposed group		Unexposed group		Total	
	No.	%	No.	%	No.	%
Females						
Dead	823	40	793	37	1,616	38
Alive	1,037	50	1,070	50	2,107	50
Lost	214	10	278	13	492	12
Total	2,074	100	2,141	100	4,215	100
Males						
Dead	715	56	963	68	1,678	62
Alive	498	39	390	27	888	33
Lost	64	5	65	5	129	5
Total	1,277	100	1,418	100	2,695	100

Efforts to obtain a date and cause of death for deceased subjects and a current address for living subjects followed methods similar to those outlined previously (6). The primary resources used were State Vital Statistics Division records, motor vehicle registries, city directories, and town residence lists that are unique to Massachusetts. Current vital status was ascertained for 88% of the women and 95% of the men (table 1). Death certificates were requested from the state of last known residence for those subjects known to have died. Death certificates were validated with the use of the subjects' names and dates of birth. Records were not available for 38 of 1,616 female deaths (2.4%) and 20 of 1,678 male deaths (1.2%).

Causes of death were abstracted from death certificates. To verify this information, we requested relevant autopsy, discharge, and pathology reports from hospitals where study subjects had died. In this manner, reported cancer deaths were confirmed for 35 and 28% of the exposed and unexposed groups, respectively. No further information was available on the remaining 67% of cancer deaths. This limited success reflects the fact that only 1,628 (49%) of all the deaths occurred in hospitals that were currently operating.

The cohort was divided into 2 exposure groups: 1) those who received air-collapse therapy with associated fluoroscopy exposure and 2) those with no record of having received this form of therapy. Two estimates of radiation exposure were calculated for the exposed group. First, the total number of air-collapse therapy

examinations, as abstracted from standard pneumotherapy logs in the medical record, were counted. Second, details of each treatment regimen (dates started and stopped, type of collapse, and side of lung collapsed) were applied to a dosimetry model to estimate the average radiation dose that would be absorbed in several target tissue organs. This model was developed for an earlier study and considered the following factors: machine exposure rate, field size, anatomical location of x-ray beam, type and mass of body tissue, and orientation of the patient during the examination (4, 7). The average number of examinations and estimated average tissue doses for the sites of primary interest are shown in table 2.

The appropriateness of the radiation dosimetry assumptions was evaluated by surveying living patients and former TB physicians. In 1981, questionnaires were mailed to all subjects with known current addresses. Up to two additional mailings and one telephone contact were made to nonrespondents, each at approximately 1-month intervals. Former patients were asked whether they had received lung-collapse therapy; how frequently a fluoroscope had been used; and whether they faced the x-ray machine, the physician, or were rotated during the fluoroscopy examination. In addition, eight mail questionnaires from 18 physicians known to have conducted air-collapse procedures in study hospitals over the appropriate time period were obtained.

Physician responses indicated that each fluoroscopy lasted 15 seconds on the average. Patient responses indicated that 25% of all fluoroscopies were performed with the patient facing the x-ray source. These data suggest that air-collapse therapy procedures were similar to those reported in a previous study of female TB patients in Massachusetts and that assumptions regarding factors in the dosimetry model were reasonable. Coefficients used for the breast dose estimations were updated from a previous report [(7) and Davis FG: Unpublished Ph.D. dissertation]. Limitations of dose estimation included a) not having individual data on the position of the patient relative to the x-ray source for that half of the population who died prior to the survey and b) not knowing with accuracy the length of fluoroscopic exposure during each examination.

Mortality analyses were conducted separately for the 4,215 females and 2,695 males eligible for study. Under-

TABLE 2.—*Number of fluoroscopy exams and dose estimates, rad, for selected organs*

Specification	Cumulative exposures				
	Females, $n=1,892$		Males, $n=1,207$		Total, $n=3,099$,[a] average
	Average	Range	Average	Range	
No. of fluoroscopy examinations	73	1–580	91	1–751	80
Estimated absorbed organ doses, rad					
Breast[b]	66	<1–627	—	—	—
Lungs	81	<1–692	108	<1–911	91
Active bone marrow	10	<1–77	15	<1–112	12

[a] 252 of the 3,351 patients having air-collapse therapy had no exposure record.
[b] Organ doses for adolescents are assumed to be equal to those of adults, except for female breast tissue.

lying cause of death was coded from death certificates according to the ICDA-8 (8). Person-years of follow-up were calculated with the use of the date of first discharge as entry date. Closing date was defined as the date of death for deceased subjects, date last known to be alive for subjects lost to follow-up, and January 1, 1981, for subjects known to be alive.

Risk estimates were standardized over 5-year age and time intervals. SMRs were calculated with the use of Massachusetts death rates to compute expected values. This was accomplished by multiplying each 5-year age and 5-year calendar time interval of a cause-specific death rate by the comparable person-years experience of the exposed individuals in that stratum and by summing the results over 5-year age and time intervals. For observed values based on 20 or fewer events, 95% Fisher exact confidence limits were computed; otherwise, 95% approximate CIs based on the Poisson distribution are reported (9). For each cause of death, a Mantel-Haenszel chi-square statistic and associated P-value were estimated (10).

Lung and breast cancer mortality data were stratified by time since exposure, age at exposure, and dose level. This analysis was restricted to patients living 10 years or more after discharge because of the long latent periods associated with these radiogenic tumors (1). Stratum-specific SMRs, CCRs (comparing the crude death rate in the exposed to the crude death rate in the unexposed), and overall sex-specific SRRS were estimated. SRRs compared the exposed group to the unexposed group, controlling for age and time at exposure. A stratified analysis was not conducted for leukemia, because few deaths were observed. For the unexposed subjects, times and ages of "exposure" were surrogate measures, estimated from dates of admission.

Proportional hazards modeling was conducted to evaluate breast cancer mortality in relation to radiation exposure, taking into account other breast cancer risk factors and/or possible confounding variables, in addition to survival time (11). Lung cancer was not evaluated by means of this technique because of the incompleteness of information on smoking history.

RESULTS

A total of 103,354 person-years of follow-up were accumulated in females for an average of 24.5 years per person. Males accumulated 56,290 person-years of follow-up for an average of 21.0 years per person. The average age when first given air-collapse therapy was 27.9 years for the 2,074 exposed women and 32.6 years for the 1,277 exposed men. The 2,141 unexposed women were, on the average, slightly older than the exposed women (32 vs. 29 yr) at their date of first discharge. The unexposed males were 11 years older on the average than the exposed males (44 vs. 33 yr) at first discharge.

Exposed females were more likely than unexposed females to have married, to have achieved a higher level of education, and to have smoked (table 3). Smoking and alcohol data, obtained from the medical record,

were missing in unequal proportions of the female exposure groups. Similar proportions of male exposure groups were smokers and users of alcohol at the time of TB hospitalization, although these data are incomplete and may not be indicative of an individual's lifetime experience. Male and female exposure groups tended to be admitted with more advanced TB and to have received more aggressive surgery, a finding consistent with the disease status of a previous Massachusetts female cohort (3). No difference in proportions between study groups was noted for race, chemotherapy treatments such as streptomycin and isoniazid, or other chronic diseases. The cohort was predominately white (96%), and their religious affiliation was mainly Catholic (62%) or Protestant (32%).

The number of deaths experienced by all women (SMR = 2.2) and all men (SMR = 1.8) in this cohort were higher than the number of deaths expected based on population rates (table 4). As anticipated, TB and respiratory diseases were major causes of death in both exposure groups. In males, significantly higher risks of death from cirrhosis of the liver (exposed group SMR = 1.7, $n = 16$; unexposed group SMR = 2.0, $n = 19$) were observed. For causes of death other than nonmalignant respiratory diseases, the mortality of both male and female exposure groups was slightly higher than that of the general population.

Cancer Mortality

There was no apparent elevation of deaths due to all types of cancer in exposed and unexposed women, although increases for some specific cancer sites were noted (table 5). Focusing on those sites of primary interest: Breast cancer mortality was similar to that expected (exposed SMR = 1.0, $n = 24$; unexposed SMR = 1.0, $n = 23$), respiratory cancer mortality was slightly elevated in both groups (exposed SMR = 1.3, $n = 10$; unexposed SMR = 1.4, $n = 11$), and leukemia mortality was modestly elevated in both groups (exposed SMR = 1.8, $n = 5$; unexposed SMR = 1.5, $n = 5$).

The risk of death in males from all cancers was elevated in the unexposed group (SMR = 1.5, $n = 159$) but not in the exposed group (SMR = 0.9, $n = 73$). There was no suggestion of an elevated risk from respiratory cancers (SMR = 0.7, $n = 16$) or leukemia (SMR = 0.4, $n = 1$) in exposed men. The number of deaths due to esophageal cancer was higher than expected (SMR = 4.2, $n = 8$), but 2 of these cases were diagnosed at the time of air-collapse therapy. Esophageal cancer was also elevated in the unexposed group and therefore may not be related to radiation exposure during TB treatment (SMR = 4.0, $n = 10$).

Breast Cancer Mortality

An increased risk of death from breast cancer was not observed. No variation in mortality by time since exposure and dose level was observed (table 6). A modest elevation was suggested for exposure during adolescence

TABLE 3.—*Distribution of selected characteristics of TB patients by gender and exposure status*

Characteristic	Females, mean		Males, mean	
	Exposed, n=2,074	Unexposed, n=2,141	Exposed, n=1,277	Unexposed, n=1,418
Year of discharge	1943	1943	1944	1946
Age at discharge, yr	28.6	32.3	33.0	44.1
Age at first exposure, yr	27.9	—	32.6	—

Specification	Females, %		Males, %	
	Exposed	Unexposed	Exposed	Unexposed
Marital status				
Never married	33	35	37	27
Married	59	52	54	57
Other	8	13	9	16
Education				
1-8 yr	18	26	15	17
9-12 yr	34	23	25	16
13 yr or more	17	11	13	8
Unknown	31	39	47	59
Smoking history				
Smoker	23	15	41	36
Nonsmoker	35	28	8	7
Unknown	43	57	51	57
Alcohol				
User	15	14	39	42
Nonuser	57	47	34	36
Unknown	28	40	27	22
Stage of TB				
Minimal	15	46	12	30
Moderate	45	31	43	36
Advanced	39	23	45	34
TB treatment				
Thoracoplasty	27	7	25	7
Lobectomy	4	4	3	4
Pneumonectomy	3	1	1	0
Streptomycin	28	30	33	36
Isoniazid	12	13	27	21

TABLE 4.—*Number of deaths observed (Obs) and expected among TB patients by gender and exposure group*

Causes of death[a]	Females				Males			
	Exposed		Unexposed		Exposed		Unexposed	
	Obs	SMR[b]	Obs	SMR[b]	Obs	SMR[b]	Obs	SMR[b]
All deaths	823	2.6*	793	1.8*	715	1.9*	963	1.7*
TB	424	82.9*	283	60.8*	263	44.4*	256	39.1*
Malignant neoplasms	100	1.1	106	1.0	73	0.9	159	1.5*
Allergic, endocrine, metabolic, and nutritional diseases	5	0.6	12	1.0	11	1.9	8	1.0
Circulatory system diseases	148	1.0	262	1.1*	206	1.0	352	1.1*
Respiratory diseases	5	3.6*	52	2.5*	70	3.0*	94	2.7*
Digestive system diseases	13	0.7	22	1.1	28	1.2	39	1.4*
Cirrhosis of liver	8	0.9	10	1.2	16	1.7*	19	2.0*
Suicide	5	1.5	6	1.9	12	1.5	3	0.4
Other and unspecified	75	2.6*	50	1.4*	52	1.7*	52	1.4*
All deaths minus TB and nonmalignant respiratory[c]	346	1.2*	458	1.1*	382	1.1*	613	1.2*

[a] ICDA-8 codes for first nine disease categories are: 010-998, 010-019, 140-209, 240-279, 390-458, 460-519, 520-577, 571, and 950-959.
[b] Ratio of observed to expected utilizes expected numbers based on 5-yr age and calendar time-specific death rates from Massachusetts.
*, P-value of <.05.
[c] Nonmalignant respiratory disease includes ICDA-8 010-019 and 460-519.

TABLE 5.—*Number of cancer deaths observed (Obs) and expected among TB patients by gender and exposure group*

Cancer type[a]	Females						Males					
	Exposed			Unexposed			Exposed			Unexposed		
	Obs	SMR[b]	95% UB[c]	Obs	SMR[b]	95% UB[c]	Obs	SMR[b]	95% UB[c]	Obs	SMR[b]	95% UB[c]
Buccal cavity and pharynx	0	0.0	2.7	3	2.1	6.1	3	0.9	2.5	11	2.4*	4.3
All digestive	22	0.9	1.3	29	0.9	1.3	27	1.0	1.5	54	1.3	1.8
Esophagus	2	2.8	10.3	0	0.0	4.3	8	4.2*	8.3	10	4.0*	7.4
Stomach	2	0.5	1.9	4	0.7	1.8	1	0.2	0.9	11	1.1	2.0
Large intestine	8	0.7	1.3	13	0.9	1.5	9	1.2	2.2	14	1.2	2.0
Rectum	2	0.7	2.6	6	1.6	3.4	2	0.6	2.1	7	1.3	2.7
Liver	3	1.1	3.2	1	0.3	1.5	3	2.4	6.7	4	2.1	5.4
Pancreas	4	1.0	2.6	2	0.4	1.5	4	0.9	2.4	6	1.1	2.4
Respiratory system	10	1.3	2.4	11	1.4	2.4	16	0.7	1.1	45	1.6*	2.2
Bone	2	4.8	17.3	0	0.0	7.2	2	5.3	18.1	1	1.6	9.3
Breast	24	1.0	1.6	23	1.0	1.4	—	—	—	—	—	—
All genital	20	1.2	1.9	20	1.1	1.8	—	—	—	—	—	—
Cervix uteri	8	1.9	3.7	8	1.8	3.6	—	—	—	—	—	—
Prostate gland	—	—	—	—	—	—	6	1.2	2.6	11	1.1	2.0
Bladder	1	0.9	5.1	1	0.6	3.3	3	1.2	3.7	6	1.4	3.1
Kidney	2	1.5	5.2	1	0.6	3.5	2	1.1	3.8	6	2.5	5.4
Brain and other central nervous system	2	0.8	3.0	3	1.3	3.8	2	0.9	3.1	4	1.9	4.7
Thyroid gland	1	2.5	13.9	1	2.1	11.1	0	0.0	18.4	0	0.0	19.1
Leukemia and aleukemia	5	1.8	4.2	5	1.5	3.2	1	0.4	2.1	5	1.4	3.2
Other and unspecified	11	0.9	1.6	9	0.7	1.3	11	1.0	1.8	16	1.3	2.1
All malignant neoplasms	100	1.1	1.3	106	1.0	1.2	73	0.9	1.2	159	1.5*	1.7

[a] ICDA-8 codes are: 140-149, 150-159, 150, 151, 153, 154, 155-156, 157, 160-163, 170, 174, 180-184, 180, 186, 188, 189, 190-192, 193, and 204-207.

[b] Ratio of observed to expected utilizes expected numbers based on 5-yr age and calendar time-specific death rates for white Massachusetts females and males. *, P-value of <.05.

[c] The upper bound (UB) of the 95% confidence limit.

with an SMR of 1.7. This effect was not apparent (CRR= 1.0) when the unexposed women were used as the comparison group.

The SRR for breast cancer mortality was 1.1 (95% CI= 0.6-2.1) when we compared the exposed to unexposed groups and controlled for time since exposure and age at exposure. This estimate is similar to that obtained by means of a proportional hazards model to control for other possible breast cancer risk factors.

Lung Cancer Mortality

When sexes were combined, no overall (SMR= 0.8 with 95% CI=0.5-1.2) or subgroup excesses of lung cancer mortality were observed (table 7). No lung cancer deaths occurred in females within 20 years of discharge. A modest elevation of risk was noted in women 20 years or more after discharge (SMR = 1.5, n= 10), an effect that was also suggested in women first exposed after age 20 (SMR= 1.5, n = 10). Excess lung cancer deaths were not observed in the male group at any time period following exposure or for any category of age at exposure. An increasing risk for death from lung cancer with increasing radiation dose, as measured by the number of exams or the estimated absorbed lung dose, was not observed in either sex when either population rates or the unexposed group were used for comparison.

The SRR for lung cancer mortality in 10-year survivors, controlling for age at exposure and time since

TABLE 6.—*Breast cancer deaths among exposed females surviving 10 years or more by the number of years after discharge, age at first exposure, and estimated exposure levels*

Specification	Number[a]	Obs	Exp[b]	SMR[c]	95% CI
No. of years after first discharge					
10-19	1,546	5	5.0	1.0	0.4-2.2
20-29	1,370	12	7.7	1.6	0.8-2.6
30-39	998	5	6.2	0.8	0.3-1.8
≥40	342	1	1.3	0.8	0.0-3.9
Age at first exposure, yr					
5-19	210	3	1.7	1.7	0.4-4.7
20-29	826	10	10.0	1.0	0.5-1.8
30-39	367	7	6.0	1.2	0.5-2.3
≥40	143	3	2.5	1.2	0.3-3.3
No. of fluoroscopy examinations					
1-99	998	15	13.2	1.1	0.7-1.8
≥100	419	6	5.3	1.1	0.5-2.4
Absorbed dose estimate for breast tissue, rad					
1-49	764	11	9.7	1.1	0.6-2.0
50-149	471	8	6.5	1.2	0.6-2.3
≥150	182	2	2.4	0.8	0.1-2.8

[a] Number of subjects; in the first section, the number of subjects entering each time interval is shown.

[b] Expected values are based on 5-yr age and calendar time-specific death rates for white Massachusetts females.

[c] Ratio of observed to expected.

TABLE 7.—*Lung cancer deaths among 10-year survivors by gender, the number of years after first discharge, age at first exposure, and exposure levels*

Specification	Females			Males			Total			
	Obs	Exp[a]	SMR[b]	Obs	Exp[a]	SMR[b]	Obs	Exp[a]	SMR[b]	95% CI
No. of years after first discharge										
10–19	0	0.9	0.0	4	3.9	1.0	4	4.8	0.8	0.2–2.1
20–29	4	2.7	1.5	4	7.3	0.6	8	10.0	0.8	0.3–1.6
30–39	4	3.1	1.3	4	7.4	0.6	8	10.5	0.8	0.3–1.5
≥40	2	0.7	2.9	1	1.7	0.6	3	2.4	1.3	0.3–3.7
Age at first exposure										
5–19	0	0.7	0.0	0	1.0	0.0	0	1.7	0.0	—
20–29	5	3.8	1.3	2	6.5	0.3	7	10.3	0.7	0.3–1.4
30–39	4	2.2	1.9	6	7.2	0.8	10	9.4	1.1	0.5–2.0
≥40	1	0.8	1.3	5	5.7	0.9	6	6.5	0.9	0.3–2.0
No. of fluoroscopy examinations										
1–99	6	4.8	1.2	4	12.0	0.3	10	16.8	0.6	0.3–1.1
≥100	3	2.0	1.5	6	7.6	0.8	9	9.6	0.9	0.4–1.8
Absorbed dose estimate for lung tissue, rad										
1–49	6	3.0	2.0	4	8.0	0.5	10	11.0	0.9	0.4–1.7
50–149	0	2.6	0.0	1	5.2	0.2	1	7.8	0.1	0.0–0.7
≥150	3	1.2	2.4	5	6.3	0.8	8	7.5	1.1	0.5–2.1

[a] Expected values are based on 5-yr age and calender time-specific death rates for white Massachusetts females and males.
[b] Ratio of observed to expected.

exposure, was 1.3 for women (95% CI = 0.5-3.4) and 0.7 for men (95% CI = 0.3-1.4).

females in this study is consistent with earlier TB studies and suggests that air-collapse therapy exposures, characterized by repeated, relatively low x-ray doses occurring over several years, may not be as carcinogenic as single or short-term exposures of the same total dose. SMRs greater than 1.2 for lung cancer could be excluded with 95% confidence, but this estimate may be distorted by differential underlying respiratory disease and smoking behavior in the exposure groups. Comparison with population rates likely underestimate risks because TB patients would have less lung tissue at risk for cancer development due to the disease itself or to surgical procedures removing all or portions of a lung. Similarly, comparisons between the exposed and nonexposed could be misleading since the exposed had more advanced disease and more frequent surgical procedures.

Leukemia has frequently been associated with radiation exposure (1). In our series, a modest risk of leukemia was found in exposed females (RR= 1.8, 95% CI= 0.6-4.2) but not in exposed males. Since the average bone marrow dose was low (12 rad) and the number of excess cases expected was small, the study did not have sufficient power to detect an effect with any meaningful precision.

Results based on a cohort defined by an underlying disease such as TB must be interpreted cautiously. An elevated cause-specific death rate in both exposure groups relative to the general population may be due to their common disease experience or some unknown correlate of that experience. In contrast, a similarly elevated rate in the exposed group relative to both the unexposed group and rates in an external population is more likely to be due to the particular experience of the exposed group. Based on very few deaths, elevated ratios

Increased risks from these three sites were not observed in an earlier TB series of females and, except for bone, risks were not consistent across gender in this cohort (4). While these sites are thought to have relatively low sensitivity to radiation (12), results of other higher dose studies have been mixed (13,14, 16, 17). Because radiation doses were low to organs outside the x-ray field, it is unlikely that radiation played a role in the etiology of these tumors.

The small nonsignificant excess of thyroid cancer in the females

TABLE 8.—*Agreement between medical record and survey data on the experience of air-collapse therapy*

Medical record information	Survey response					
	Exposed group		Unexposed group		Total	
	No.	%	No.	%	No.	%
Females[a]						
Exposed	564	92	47	8	611	100
Unexposed	46	8	519	92	565	100
Males[b]						
Exposed	288	90	32	10	320	100
Unexposed	10	5	193	95	203	100

[a] Kappa statistic K=0.84, $P<.001$.
[b] Kappa statistic K=0.83, $P<.001$.

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